MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Adrenergic Antagonists

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

By the end of this lecture, students should be able to:

Chapter 1

✓ Outline the mechanisms of action of adrenergic neuron blockers.
✓ Classify a-receptor blockers into selective & non-selective.
✓ Know the pharmacokinetic aspects & pharmacodynamic effects of adrenergic blockers.
✓ Identify the specific uses of non selective and selective a-adrenergic blockers.

Chapter 2

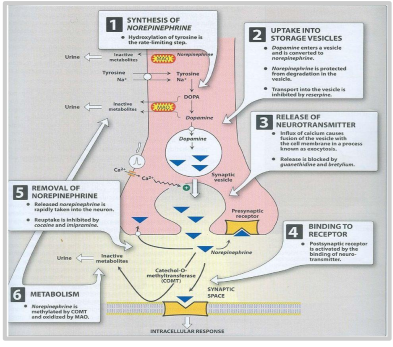
✓Outline the mechanisms of action of B-blockers.
✓Classify B-receptor blockers into selective & non-selective.
✓Know the pharmacokinetic aspects & pharmacodynamic effects of B-adrenergic blockers.
✓Identify the specific uses of non selective and selective B -adrenergic blockers.

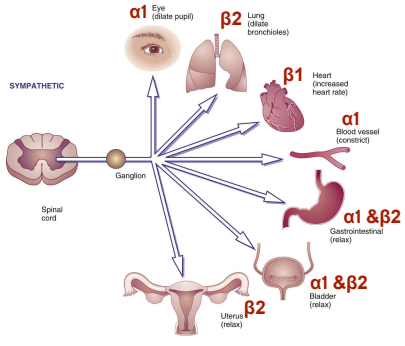
Editing File

Review "just for better understanding"

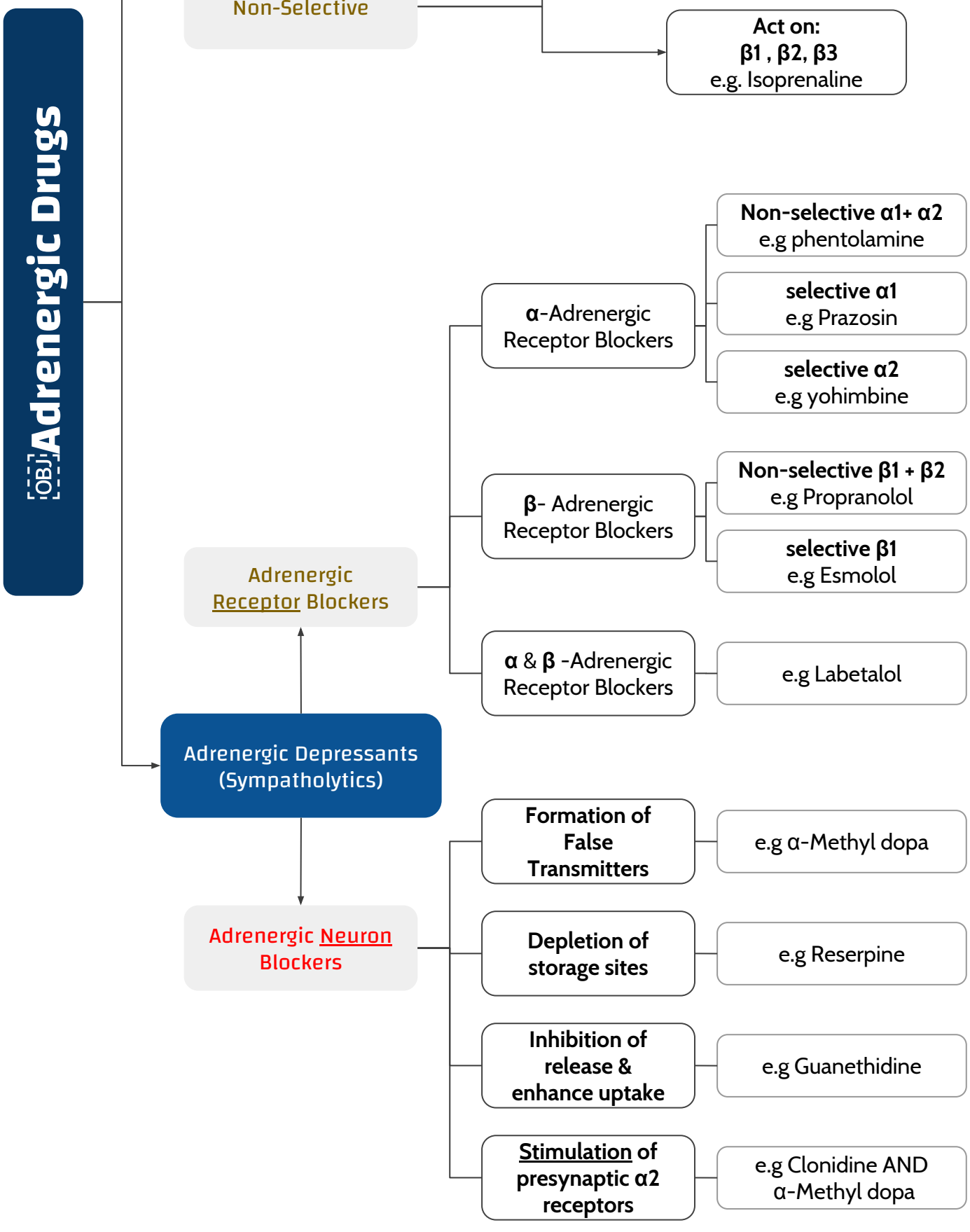
α1	β2	β1	β3
Post-synaptic located in tissue (meaning it is mediated by a neuron which received a signal from a preganglionic neuron by synapsis)			
excitatory in function (cause contraction) except in GIT	inhibitory in function (cause relaxation)	excitatory in function, present mainly in heart, juxtaglomerular cells of the kidney	In adipose tissue
Present mainly in smooth muscles		↑ heart rate: chronotropic effect (Tachycardia) ↑ force of contraction : + inotropic effect Increase cardiac output ↑ conduction velocity: + dromotropic effect (via A.V. node)(**dromotropic** effect means an effect in the speed of conduction of electrical impulses) ↑ blood pressure ↑ renin release (this is an enzyme produced by the kidney in response to stretch receptors found on blood vessels, its function is to increase blood pressure)	↑ lipolysis ↑ free fatty acids
Contraction of pregnant uterus	Relaxation of the uterus (Delay premature labor) also called tocolytic effect		
Vasoconstriction of skin & peripheral blood vessels → increased peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension. Agonists used as nasal decongestants.	Relaxation of skeletal & coronary blood vessels (vasodilatation)		
Relaxation of GIT muscles & urinary bladder's muscles. Contraction of GIT sphincter (constipation) & urinary bladder's sphincter urinary retention			
Contraction of radial muscle of eye causes active mydriasis, (dilation of pupil, cholinergic agents have no effect on this muscle)	.Relaxation of bronchial smooth muscles (bronchodilation) .Tremor of skeletal muscles		
Increase blood glucose level (hyperglycemia), by:			
.↑ glycogenolysis	.↑ glucagon release from pancreas .↑ liver & muscle glycogenolysis		

α2	β2
Pre-synaptic	
Inhibition of norepinephrine release (negative feedback mechanism) How? this mainly happen by an autoreceptor 'presynaptic receptor' which is present on the neuron releasing the neurotransmitter itself, the neurotransmitter bind to the receptor of the same neuron it was released by and inhibiting further release of the neurotransmitter, producing a negative feedback mechanism	Increase **release** of norepinephrine (Positive feedback mechanism)



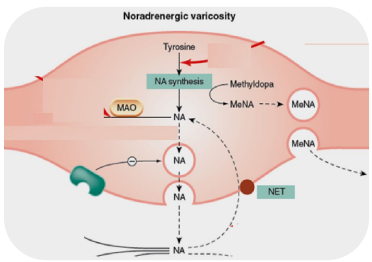
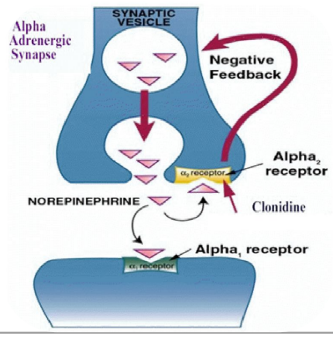


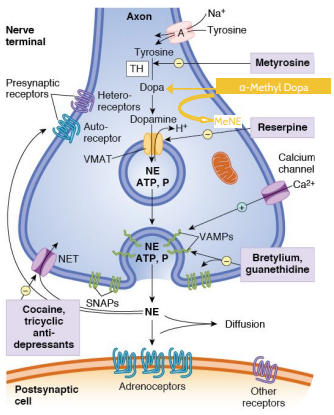
overview

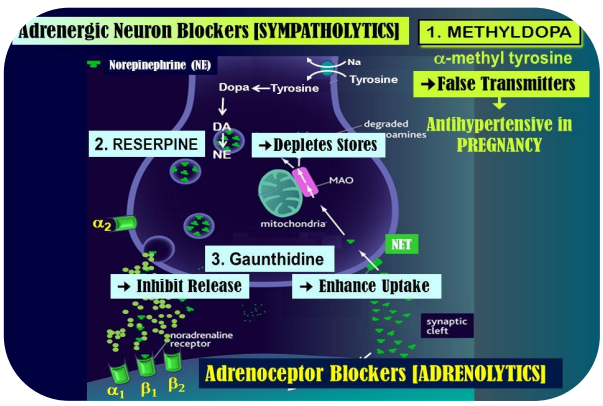

Adrenergic Drugs
Review to refresh your mind
Adrenergic Stimulants (Sympathomimetics)
Selective
Act on: α1
e.g. Phenylephrine
Act on: β1
e.g. Dobutamine
Non-Selective
Act on: α1, α2 , β1 , β2, β3
e.g. Adrenaline
Act on: β1 , β2, β3
e.g. Isoprenaline
Adrenergic Depressants (Sympatholytics)
Adrenergic Receptor Blockers
α-Adrenergic Receptor Blockers
Non-selective α1+ α2
e.g phentolamine
selective α1
e.g Prazosin
selective α2
e.g yohimbine
β- Adrenergic Receptor Blockers
Non-selective β1 + β2
e.g Propranolol
selective β1
e.g Esmolol
α & β -Adrenergic Receptor Blockers
e.g Labetalol
Adrenergic Neuron Blockers
Formation of False Transmitters
e.g α-Methyl dopa
Depletion of storage sites
e.g Reserpine
Inhibition of release & enhance uptake
e.g Guanethidine
Stimulation of presynaptic α2 receptors
e.g Clonidine AND α-Methyl dopa

Chapter 1 : α Adrenergic Antagonists

Adrenergic Neuron Blockers Drugs

	α-Methyl Dopa	Clonidine	Apraclonidine
Action	-Forms false transmitter that is released instead of NE "α-methylnoradrenaline replaces NE in vesicles" -Centrally acting a2 adrenergic agonist that inhibits NE release "Can cross BBB" 	-Central a2 receptor agonist to inhibit NE release -Suppresses sympathetic outflow activity from the brain 	Acts by decreasing aqueous humor formation.
Uses	- Drug of choice in treatment of hypertension in pregnancy (gestational hypertension, pre- eclampsia "disorder of pregnancy characterized by proteinuria and rise in BP") "NO teratogenic effect "	- Little use as antihypertensive agent due to rebound hypertension upon abrupt withdrawal. "side effect" "Extra: Clonidine causes downregulation of a2 receptors, but its efficacy as an a2 agonist compensates for the decreased receptors. Therefore in withdrawal physiological neurotransmitters fail to produce the same effect, and due to poor stimulation of a2 receptors rebound hypertension occurs"	Open angle glaucoma as eye drops (topical)





Adrenergic Receptors Blockers

Classification of α-receptor Antagonists

selective α1- antagonists

e.g.
- prazosin
- doxazosin
- terazosin

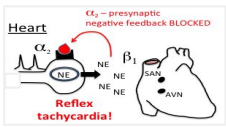
Non-selective α antagonists

e.g.
- phenoxybenzamine
- phentolamine

Selective α2-adrenoceptor

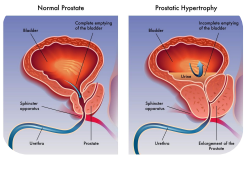
e.g.
- yohimbine

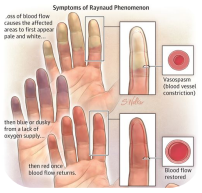
Non-Selective α-Receptor Blockers

	Phentolamine	Phenoxybenzamine
MOA	Non-selective antagonists of both α1 & α2 receptors.	
P.K	• Reversible block of both α1 & α2 receptors."non-covalent bond so less duration of action" • Short acting (4 hrs)	• Irreversible blocking of α1 & α2 receptors."by covalent bond" • Long-acting (24 hrs)
Pharmacological actions	• Increase cardiac output (α2 block) • Decrease peripheral vascular resistance. • Postural (orthostatic) hypotension. "due to baroreceptor reflex, pull of gravity and reduced BP contribute to low venous return which causes hypotension when standing" • Reflex tachycardia due to fall in B.P, mediated by baroreceptor reflex and due to block α2 in heart.	
Indication	In **Pheochromocytoma** : Should be given before surgical removal to protect against hypertensive crisis. (pheochromocytoma is a tumor of the adrenal medulla that causes an excessive release of NA "synthesized in the medulla", resulting in an overstimulation of a1 receptors, resulting in hypertension)	
ADRs	• Headache • Nasal stuffiness or congestion • Vertigo & drowsiness " caused by the hypotension" • Male sexual dysfunction (Inhibits ejaculation) • Tachycardia . • Postural hypotension.	
Contradiction	Patients with decreased coronary perfusion, because both drugs can precipitate arrhythmias and angina.	

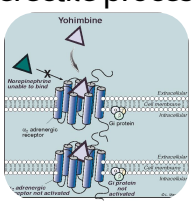
Selective α1 - adrenoceptor Antagonists

	• Prazosin • Doxazosin• Terazosin
MOA	Selective α1 -adrenoceptor Antagonists
P.K	• Prazosin has short half-life. • Doxazosin, terazosin have long half lives.
Pharmacological actions	• Vasodilation due to relaxation of arterial and venous smooth muscles. • Fall in arterial pressure with less reflex tachycardia than with non-selective α- blockers. • First dose may produce an orthostatic hypotensive response that can result in syncope and fainting.
Indication	• Treatment of essential hypertension WITH prostate enlargement.(Hypertrophy) • Urinary obstruction associated with benign prostatic hyperplasia (BPH). • Raynaud's disease causes some areas of your body such as your fingers and toes to feel numb and cold in response to cold temperatures or stress.





Selective α1A & Selective α2 Antagonists

	Selective α1A	Selective α2
Drugs	**Tamsulosin**	**Yohimbine**
MOA	• Relaxation of smooth muscles of bladder neck & prostate →improve urine flow. • Has minimal effect on blood pressure.	Increase nitric oxide "NO" released in the corpus cavernosum thus producing vasodilator action and contributing to the erectile process. 
Indication	Treatment of benign prostatic hypertrophy (BPH).	Used as aphrodisiac in the treatment of erectile dysfunction.
ADRs	As before with non selective but to a lesser degree.	———————-

β- Adrenoceptors Blockers

Pharmacodynamic Classifications:

According to selectivity		
Non-selective "β1 & β2" "Mnemonic=POST"	Selective "β1"	Mixed "β & α" act on α1 and classes of β :β1,β2,β3"
Propranolol	Atenolol	Labetalol
Pindolol	Bisoprolol	
	Metoprolol	
Sotalol	Esmolol	
Timolol	Acebutolol	Carvedilol
	Betaxolol	
Oxprenolol	Celiprolol	

According to presence of agonistic/antagonistic action Intrinsic Sympathomimetic Activity (ISA)	
Without ISA	With ISA "adrenergic partial agonists"
Atenolol	Labetalol
Bisoprolol	
Metoprolol	Acebutolol
Propranolol	
Sotalol	Pindolol
Timolol	
Carvedilol	Oxprenolol

According to presence of membrane stabilizing effects	
Drugs	Effects
Propranolol	-Block Na Channels -Quinidine-like action -Antiarrhythmic action "Local anesthetic"
labetalol	

Pharmacokinetic Classification:

According to lipid solubility		
	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
T 1/2 "Most of them 3-10 Hrs"	Short	Long **Except** Esmolol → 10 min & given intravenously.
CNS side effects	Cross BBB, High depressant actions Sedative effect →↓ anxiety	Low
Drugs	**Metoprolol / Propranolol** **Timolol / Labetalol** **Carvedilol**	**Atenolol / Bisoprolol** **Esmolol / Sotalol**

Pharmacological actions:

CVS

- Negative (inotropic, chronotropic, dromotropic) → ↓ Cardiac Output

Antianginal effects (ischemic heart disease):
- ↓ Heart rate (Bradycardia) → ↓ Oxygen consumption
- ↓ Force of contraction → ↓ Cardiac work

Antiarrhythmic effects: (class II)
- ↓ Excitability, ↓ automaticity & ↓conductivity

Due to its sympathetic blocking.

Blood pressure:
Antihypertensive →↓BP in hypertensive patients due to effects on:
- Inhibiting heart properties →↓ cardiac output (β1)
- β Blockade ↓renin secretion ↓Angiotensin II & aldosterone secretion (β1)
- Presynaptic inhibition of norepinephrine release from adrenergic nerves

Blood vessels β2:
- Increase Peripheral resistance (PR) by blocking vasodilatory effect β2
- ↓ Blood flow to organs → cold extremities

contraindicated in Raynaud's disease.

Respiratory tract β2

- Bronchoconstriction

contraindicated in asthmatic patients.

Eye

- ↓ Aqueous humor production from ciliary body
- ↓ Intraocular pressure (IOP)

E.g. timolol as eye drops for glaucoma.

Metabolic effects & Intestine

- Hypoglycemia by: ↓ glycogenolysis in liver & ↓ glucagon secretion in pancreas.
- lipolysis in adipocytes
- Na+ retention secondary to ↓blood pressure → ↓ renal perfusion
- Increase Intestinal motility.

Clinical uses:

Cardiovascular disorders

Propranolol
Atenolol "Preferred in regular treatment of hypertension"
Bisoprolol
Labetalol: α & β blockers in hypertensive pregnant & hypertensive crisis.

Hypertension

Bisoprolol
carvedilol

In supraventricular "chambers above ventricles" & ventricular arrhythmias.

cardiac arrhythmias

↓ Heart rate, ↓ cardiac work & oxygen demand.

↓ The frequency of angina episodes.

Angina pectoris

Carvedilol
Antioxidant "decrease formation of free radicals" and **non selective α & β** blocker.
↓ Myocardial remodeling & risk of sudden death.

Congestive heart failure

"Myocardial remodeling =hypertrophy ,hyperplasia and increase apoptosis of cardiac muscle cells after injury"

Cardio-protective effect
- ↓ infarct size "infarct: dead tissue due to an ischemic process"
- ↓ morbidity & mortality → ↓myocardial O2 demand.
- Anti-arrhythmic action.
- ↓ Incidence of sudden death.

Myocardial infarction

Other disorders

Used with **α**-blockers
never alone
- **α-blockers** lower the elevated blood pressure.
- **β-blockers** protect the heart from norepinephrine.

Pheochromocytoma

Timolol as eye drops

↓ secretion of aqueous humor by ciliary body.

↓ Intraocular pressure (IOP)

Chronic glaucoma

Thyrotoxicosis
- Protect the heart against sympathetic overstimulation.
- Controls symptoms; Tachycardia, tremors and sweating.

Hyperthyroidism

"Thyroid hormone causes sympathetic stimulation in numerous organs especially the heart, so can be avoided by beta block."

Propranolol
Prophylactic
↓ episodes of chronic migraine.
↓ catecholamine-induced vasodilatation in the brain vasculature.

Migraine

Propranolol
-Social and performance type.
-Controls symptoms due to sympathetic system stimulation as tachycardia, tremors, sweating.

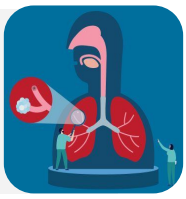
Anxiety

Adverse effects:

Due to blockade of β1-receptor:

- ➔ Bradycardia
- ➔ Hypotension
- ➔ Heart failure

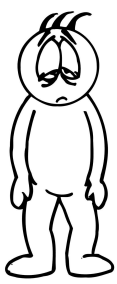
Due to blockade of β2-receptor:

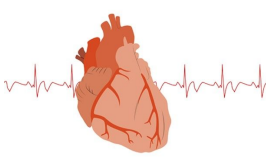


- ➔ Hypoglycemia.
- ➔ ↑ Triglyceride → hypertriglyceridemia.
- ➔ Bronchoconstriction.
- ➔ cold extremities & intermittent claudication (due to vasoconstriction).
- ➔ Erectile dysfunction & impotence except Nebivolol will increase NO .
- ➔ Coronary spasm in variant angina patients.

All β adrenergic blockers

- ➔ Mask hypoglycemic manifestations in diabetic patients "Delay the recovery of hypoglycemia " → COMA.
- ➔ Depression and hallucinations.
- ➔ Gastrointestinal disturbances.
- ➔ Sodium retention, due to reduced renal perfusion which is secondary to hypotension.
- ➔ Fatigue.





Precautions

- ➔ **Sudden stoppage will give rise to a withdrawal syndrome:** Rebound angina, arrhythmia, myocardial infarction & Hypertension.
- ➔ This is due to Up-regulation of β-receptors. "Increase numbers of β receptor " To prevent withdrawal manifestations → drug withdrawn gradually.

Contraindications:

safer with cardio-selective β-blockers

Peripheral vascular disease e.g: Raynaud's	Hypotension	Diabetes GIVEN CAUTIOUSLY
Bronchial Asthma	Heart Block	**Alone in** Pheochromocytoma "must be given with an α-blockers"

	Propranolol
MOA	- Non-Selective **β1 & β2** blockers. - Membrane stabilizing action. - Quinidine-like. - No ISA , but have sedative action
P.K	Lipophilic: - Completely absorbed. - **70%** destroyed during first pass hepatic metabolism. - **90-95%** protein bound. - Cross BBB and excreted in urine. - Can be given Orally (P.O) or parenteral.
Pharmacological actions	**β**-blocking Effect: **1- Antiarrhythmic effects:** Membrane Stabilization: Block Na channels → direct depressant to myocardium → has local anesthetic effect. **2- CNS Effect:** Sedative action **3- antihypertensive**: same as previously mentioned + inhibiting sympathetic outflow in CNS **β1**-blocking Effect: 1- Inhibit heart properties → ↓cardiac output. 2- Anti-ischemic action 3- Antiarrhythmic effect **β2**-blocking Effect: **1-Metabolism:** In skeletal muscles: ↓glycolysis , in liver:↓ glycogenolysis & in pancreas: ↓ glucagon secretion. 2- Cause vasoconstriction + Bronchospasm + Increase Intestinal motility.
Indication	- Hypertension - Arrhythmias - Angina - Myocardial infarction - Migraine (Prophylaxis). - Pheochromocytoma used with **α**-blockers (never alone). - Chronic glaucoma. - Tremors. - Anxiety (social & performance). - Hyperthyroidism.

	Carvedilol	Labetalol
MOA	- Non-Selective **α1 & β** blockers - Without ISA - Antioxidant action	- Non-Selective **α1 & β** blockers - Rapid acting - With ISA= characterizes a group of beta blockers that are able to stimulate beta-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way. - Produce peripheral vasodilation - Decrease blood pressure
Indication	Congestive heart failure reverses its pathophysiological changes.	- Severe hypertension in pheochromocytoma - Hypertensive crisis (e.g. during abrupt withdrawal of clonidine). - Used in pregnancy-induced hypertension
ADR	Orthostatic hypotension Edema	Orthostatic hypotension (postural hypotension) Sedation & dizziness

Summary

Drug	Act on	Uses
α-Methyl Dopa	Neuron	- hypertension in pregnancy - pre-eclampsia - gestational hypertension
Clonidine		-Management of withdrawal symptoms - Little use as antihypertensive agent due rebound hypertension upon abrupt withdrawal
Apraclonidine		Open angle glaucoma as eye drops
Phenoxybenzamine and Phentolamine	α1 and α2 (non-selective)	Before removal of Pheochromocytoma to prevent Hypertensive Crisis.
Prazosin, doxazosin and terazosin	α1 (Selective)	- Treatment of essential hypertension. - Urinary obstruction associated with benign prostatic hyperplasia (BPH) - Raynaud's disease.
Tamsulosin	α1A (more selective)	benign prostatic hypertrophy (BPH)
Yohimbine	α2 (selective)	Used as aphrodisiac in the treatment of erectile dysfunction
Drug	**Act on ....**	**Uses**
Propranolol	β1 and β2 (non-selective)	-Migraine prophylaxis -Hyperthyroidism - Social anxiety
Timolol		Glaucoma
Atenolol , Bisoprolol and Metoprolol	β1	-Myocardial infarction -Hypertension
Esmolol Ultra short acting		Cardiac arrhythmia
Carvedilol	α and β	Congestive heart failure
Labetalol		-Hypertension in pregnancy -Hypertensive emergency

QUIZ

MCQ

1- A new antihypertensive drug was tested in an animal model of hypertension. The drug when given alone reduces blood pressure in the animal. Norepinephrine when given in the presence of this drug did not cause any significant change in blood pressure or heart rate in the animal. The mechanism of action of the new drug is similar to which of the following agents?

A-Doxazosin B-Atenolol C-Carvedilol

2- A beta blocker was prescribed for hypertension in a patient with asthma. After a week of treatment, the asthma attacks got worse, and the patient was asked to stop taking the beta blocker. Which beta blocker would you suggest as an alternative that is less likely to worsen the asthma?

A-Metoprolol B-Propranolol C-Labetalol

3- A 70-year-old male is treated with doxazosin for overflow incontinence due to his enlarged prostate. He complains of dizzy spells while getting up from bed at night. Which drug would you suggest as an alternative that may not cause dizziness?

A-Propranolol B-Phentolamine C-Tamsulosin

4- Which of the following drugs is commonly used topically in the treatment of glaucoma?

A-Esmolol B-Timolol C-Yohimbine

5- Which of the following is correct regarding alpha adrenergic blockers?

A-Alpha adrenergic blockers are used in the treatment of hypotension in anaphylactic shock.
B-Alpha adrenergic blockers may cause bradycardia.
C-Alpha adrenergic blockers are used in the treatment of benign prostatic hyperplasia (BPH)

1-C 2-A 3-C 4-B 5-C

SAQ

1-2.A 50-year-old male was brought to the emergency room after being stung by a hornet. The patient was found to be in anaphylactic shock, and the medical team tried to reverse the bronchoconstriction and hypotension using epinephrine. However, the patient did not fully respond to the epinephrine treatment. The patient's wife mentioned that he is taking a prescription medication of his blood pressure, the name of which she does not remember.

Q1.Which of the adrenergic antagonist medications is he most likely taking that could have prevented the effects of epinephrine?

Q2.What is the mechanism of action of that drug?

Q3.A 70-year-old male needs to be treated with an α-blocker for overflow incontinence due to his enlarged prostate. Which drug would you suggest in this patent that will not affect his blood pressure significantly?

Q4.A 32-year-old pregnant female was brought to the ER, after investigations she was diagnosed with Gestational Hypertension.What is the drug of choice of this case?

Q5.A 82 year old man with history of Angina and hypertension presented to the ER with tachycardia. Which adrenergic antagonist drug should be prescribed to this patient?

1-Propranolol 2-Non selective β1, β2 blocker 3-Tamsulosin 4- α-Methyl dopa 5-Doxazosin

pharmacology

Team 438

GOOD LUCK

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Share with us your ideas !